Even if treatment does not rid the patient of parasites it may give benefit in that some adult worms will probably have been killed and the rate of deposition of eggs in the tissues will have been reduced. Perhaps the risk of the crippling sequelae of bilharziasis will be lowered if, in the absence of cure, the output of eggs can be restricted to a much reduced level. Consequently, in evaluating the effectiveness of drugs some workers are studying the egg output in addition to the "cure rate." This entails the quantitative estimation of the patient's egg load before and after treatment, and while this method may be considered time-consuming it does enable the "degree of cure" to be determined and to be compared with intensity of infection.

The concept of suppressive therapy with spaced treatments —and generally reduced side-effects—has been extensively investigated in recent years. The drugs chiefly used have been sodium antimony dimercaptosuccinate (TWSb) and more recently bucanthone hydrochloride. D. M. Forsyth[2] has recently drawn attention to the "shift" of worms under the influence of antimony. Suppressive therapy was more successful in treating infections by *S. haematobium* than by *S. mansoni,* and it is considered that this might be due to the movement of worms in response to the drug. The adult worms of *S. haematobium* are thought to migrate from the blood-vessels of the urinary tract to the lungs. They may be immobilized there and their breeding be reduced. But the adult worms of *S. mansoni* are believed to migrate to the liver, whence return is easy to the mesenteric veins if drug treatment is not maintained. The search for new drugs has received fresh stimulus from biochemical studies of the schistosome and its food requirements. When these are known it is possible that the way may be open for the development of drugs by better-informed methods than at present, thus eliminating the empirical screening of thousands of substances for schistosomicidal action.

A paper by Dr. P. Jordan in the *B.M.J.* this week (page 276) reports on a trial in Tanzania of a new drug for the treatment of *S. mansoni* infection. Designated Ciba 32,644-Ba, and since publicized as Ambilhar, the drug appeared to be less effective than TWSb, though in higher doses it may prove to be more so. In addition a letter appears from Professor A. W. Woodruff (page 291) in which he is rightly critical of the recent publicizing of Ambilhar in the lay press despite a lack of reports in scientific periodicals of its effectiveness. This kind of publicity is indeed disconcerting, and it becomes even more so when one of the first papers to give a clinical evaluation of the drug suggests it may be less satisfactory than drugs already in use.

Spinach—a Risk to Babies

Though traditionally regarded as a healthy and even invigorating vegetable, spinach may have some hazards after all. A. Sinios and W. Wodsak have recently given an account[1] of 14 children in Germany who developed methaemoglobinaemia after eating it.

Methaemoglobinaemia is one of the causes of cyanosis ; it may occur as a genetic defect[2 3] or as a result of treatment with acetanilide, phenazone, phenacetin, or nitrites. Nitrates taken in the food or for therapeutic reasons may be converted into nitrites by the action of the intestinal bacterial flora,[4] and the condition may also be caused by aniline derivatives and potassium chlorate.

In methaemoglobinaemia the ferrous porphyrin complex is oxidized to the ferric form, which cannot combine with oxygen and is useless for respiration. The methaemoglobin concentration in the blood is normally kept at a level of 1.7 g./100 ml. by constant reduction.[5] If it rises above this level from any cause reduction may be achieved by a slow intravenous injection of a 1% aqueous solution of methylene blue in a dosage not exceeding 1 mg. per kg. body weight or by ascorbic acid by mouth.

Agents causing methaemoglobinaemia are less well tolerated in early life than later.[6] In the newborn baby foetal haemoglobin accounts for 60–80% of the total haemoglobin, but by the age of 3 months only 30% remains.[7 8] Foetal haemoglobin is much more readily oxidized to methaemoglobin than is adult haemoglobin. Infants are also at risk because of a temporary deficiency of methaemoglobin reductase or of its co-enzyme, reduced diphosphopyridine nucleotide, which is normally generated by glycolysis in the red cell.[9]

Fresh spinach contains up to 180 mg. nitrate per 100 g., but no nitrite. Nitrates are found in higher concentrations in spinach grown in beds fertilized with manure. In 24–48 hours after gathering the leaves the nitrate content falls and nitrites increase up to 66 mg. per 100 g. In fresh frozen spinach nitrites appear on thawing, but the content is low in baby food sold in glass jars. During cooking about 80% of the nitrate is dissolved, but in Germany the water is often used for making spinach purée.[1] This practice is uncommon in Great Britain, where cookery books and books on dietetics advise draining and pressing the spinach after cooking.

The children described by Sinios and Wodsak were aged between 2 and 10 months and developed their methaemoglobinaemia after eating spinach which was rich in nitrites. In 12 of the cases spinach had been bought fresh. Poisoning occurred from eating the purée and in two cases from drinking the water in which the spinach had been cooked. Spinach taken soon after preparation did not cause cyanosis in 12 cases, but it developed one to three hours after a meal of spinach kept for 24 to 48 hours, in four cases at room temperature and in five others in the refrigerator. In seven cases the mother found no alteration in the taste of the spinach. One baby with a methaemoglobin concentration of 80% died soon after admission to hospital.

The symptoms depended on the amount of nitrite absorbed, and varied from grey-pale cyanosis in mild cases to rapid pulse and respiration and muddy cyanosis in severe cases. Most of the babies continued to smile and play, but a few collapsed. Vomiting and diarrhoea were probably the result of the action of nitrites on the stomach and intestines. The chocolate colour of the blood was striking and persisted after oxygen was passed through the samples.

The reduction of nitrates to nitrites must have occurred mainly during the storage of spinach, since the first meal did

1 Sinios, A., and Wodsak, W., *Dtsch. med. Wschr.*, 1965, **90**, 1856.
2 Newcombe, C. P., and Dawson, J., *Brit. med. J.*, 1958, **1**, 1396.
3 Gerald, P. S., "The Hereditary Methemoglobinemias," in *The Metabolic Basis of Inherited Disease*, 1960, p. 1068. New York.
4 Knotek, Z., and Schmidt, P., *Pediatrics*, 1964, **34**, 78.
5 Lemberg, R., and Legge, J. W., *Hematin Compounds and Bile Pigments*, 1949, p. 518. New York.
6 Kübler, W., *Dtsch. med. Wschr.*, 1965, **90**, 1881.
7 Pisciotta, A. V., Ebbe, S. N., and Hinz, J. E., *J. Lab. clin. Med.*, 1959, **54**, 73.
8 Künzer, W., and Schneider, D., *Acta haemat.*, 1953, **9**, 346.
9 Ross, J. D., and Desforges, J. F., *Pediatrics*, 1959, **23**, 718.

not cause the damage. Even nitrate-rich spinach, when eaten fresh, is tolerated well by babies, but water rich in nitrate often causes methaemoglobinaemia. In the two cases in which methaemoglobinaemia developed within two hours of the meal it is probable that the raw spinach contained an excess of nitrite, possibly owing to inefficient and too tight storage during transport.

The amount of nitrite absorbed cannot be assessed by estimating the methaemoglobin concentration. Aspiration of stomach contents reveals spinach up to eight hours after a meal, and it serves the therapeutic purpose of preventing further absorption of nitrites. The haemoglobin becomes normal 12 to 14 hours later.

Laboratory Control of Anticoagulants

Though oral anticoagulants have been in general use for over 20 years, the laboratory control of treatment with them is still in some confusion. This uncertainty is a hazard to patients as well as a handicap to investigators studying the most effective use of these drugs.

The prothrombin-time test devised by A. J. Quick[1] has been the technique used almost universally for control since coumarin-type anticoagulants became available. The test was not designed for this purpose but proved to be a sensitive detector of the defect in coagulation produced by oral anticoagulants. The delightful simplicity of the method, which consists in the addition of a tissue extract (thromboplastin) to blood to speed up its clotting-time from a matter of minutes to one of seconds, more than compensates for its disadvantages. Later techniques, such as the prothrombin and proconvertin (P & P) test,[2] Thrombotest,[3] and others[4 5] have had only limited appeal and give different results with the same blood.

Unfortunately, widespread adoption of the Quick test has given no uniformity in methods of control of treatment. Different ways of expressing results—whether as prothrombin activity, ratio, or index—as well as different types of dilution curves have caused confusion and have resulted in different levels of anticoagulation being considered "therapeutic." Many types of tissue extract derived from human or animal sources are in use. Some pathologists make their own preparation from necropsy tissue, but the majority prefer to purchase commercial extracts of animal tissue. The most serious aspect of these variations in laboratory methods is that remarkable differences in results are obtained with the same patient's blood, even when everything else is standardized, simply by substituting different commercial thromboplastins in the Quick test.[6–8]

L. Poller[9] studied the main reagents at present marketed in Great Britain and some hospital preparations. The blood of a series of patients on anticoagulant treatment was tested simultaneously with the different thromboplastins. The average prothrombin activity varied between 14% and 40% with the different products, individual bloods showing even greater variations due to differences in the sensitivity of the reagents to depression of clotting factors.

Many hospitals prefer the term "ratio" to "activity." This is the relation of the patient's prothrombin time to a control. These ratios varied over a wide range between 1.3 and 2.4 and appeared even less reliable. In other words, if the conventional therapeutic ranges of 15–30% activity or 2–3 times ratio were used, the coagulation defect with some of the reagents would be homoeopathic and with others potentially dangerous. Some manufacturers give no recommendations on a therapeutic range with their product and others give no firm grounds for the range recommended. One British manufacturer produces two reagents for the Quick test which give different results. To this we may add the knowledge that the manufacturers as well as individual hospital pathologists have great difficulty in producing reagents which give reproducible results between successive batches in the absence of an outside standard.

What effect does all this have on an individual patient's treatment? The amount of drug prescribed will reflect the laboratory technique employed and may well alter the outcome of the anticoagulant treatment. If the patient is discharged from hospital on long-term therapy there may be great difficulty in laboratory control if he moves out of range of his local hospital. The decision on the value of anticoagulants for his condition will have been decided by reference to clinical trials, which may be irrelevant if the dosage of anticoagulants is controlled by a different method. In fact few papers from the vast literature on anticoagulants have paid anything but scant attention to laboratory methods and their implications in determining dosage.

Two promising moves, one national and the other international, have been made to tackle the problem. In the Manchester Regional Hospital Board area a voluntary scheme has been established from Withington Hospital in co-operation with the pathologists for the supply of a standard thromboplastin for routine and research purposes.[9] Considerable economy has resulted from the scheme there because of the high cost of some of the commercial extracts previously in use. With the net saving it has been possible to subsidize routine or periodic supplies of a standard to hospitals outside the region. A recent report shows that nearly a third of the hospitals in the country are co-operating in the project.[10] At a meeting held earlier this year at Withington an effort was made to persuade the representatives of the major manufacturers of the urgent need to standardize their efforts, and a start has been made. Work of this kind should not be the responsibility of a single regional board, and the extension of the standard to the rest of the hospitals in the country cannot be expected to proceed while the cost of the administration of the scheme is borne by the Manchester Board alone.

The international move is the establishment of an expert panel to consider standardizing laboratory control of anticoagulants under the auspices of the International Committee for the Standardization of Methods in Haematology.[11] There are enormous difficulties to international agreement in this complex field. But success is essential. It will be attained only through co-operation between clinicians, pathologists, and manufacturers.

[1] Quick, A. J., *J. biol. Chem.*, 1935, **109**, lxxiii.
[2] Owren, P. A., and Aas, K., *Scand. J. clin. Lab. Invest.*, 1951, **3**, 201.
[3] —— *Lancet*, 1959, **2**, 754.
[4] Denson, K. W., *J. med. Lab. Technol.*, 1961, **18**, 257.
[5] Poller, L., *J. clin. Path.*, 1963, **16**, 89.
[6] —— *Acta Haemat. (Basel)*, 1964, **32**, 292.
[7] Hougie, C., *Fundamentals of Blood Coagulation*, 1963. New York.
[8] Biggs, R., *Genetics and Interaction of Blood Clotting Factors*, 1965. Stuttgart, p. 303.
[9] Poller, L., *Brit. med. J.*, 1964, **2**, 565.
[10] *The Laboratory Control of Anticoagulants*, 1965, Thrombosis Research Fund, Withington Hospital, p. 5.
[11] *Brit. med. J.*, 1965, **2**, 1133.